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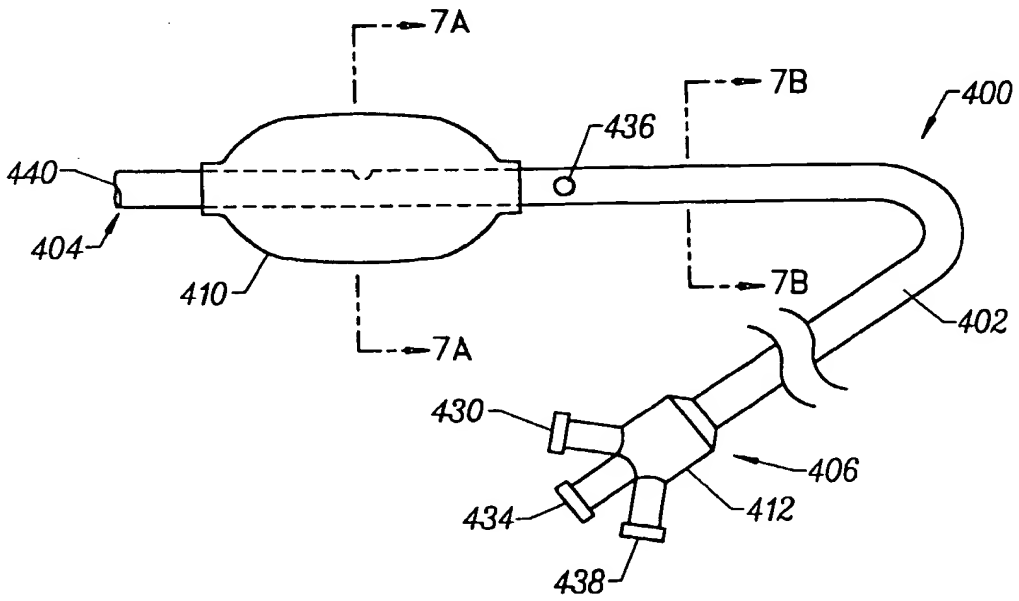


(57) Abstract: Methods and sytems for exchanging endogenous cerebrospinal fluid (CSF) with a CSF replacement fluid are described (Fig. 9). The methods comprised identifying patients having a deleterious or contaminating substance in the CSF of a CSF space, infusing a CSF replacement fluid, and removing an equivalent volume of endogenous CSF. Such methods can reduce the concentrations of the deleterious or contaminating substance to an arbitrarily low volume. Systems comprised one or more implanted catheters together with flow control mechanisms (402) for delivering the CSF replacement fluid to a patient and removing the endogenous CSF (7 A). The systems may include single catheters with single lumens for sequential infusion and removal (12). Alternatively, these systems may employ at least two lumens present in one or two catheters in order to simultaneously infuse and remove CSF.

# SYSTEMS AND METHODS FOR EXCHANGING CEREBROSPINAL FLUID

## BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates generally to medical devices and methods. More particularly, the present invention relates to devices, systems, methods, and kits for exchanging endogenous cerebrospinal fluid (CSF) with a CSF replacement fluid.

The brain and spinal cord are bathed in cerebrospinal fluid (CSF) and encased within the cranium and vertebral column inside a thin membrane known as the meninges (Fig. 1A). The space within the meninges includes the subarachnoid space SAS, the ventricles (including the lateral ventricle LV, third ventricle 3V, and fourth ventricle 4V), the vertebral column, and the brain interstitial spaces, and is referred to herein as the "CSF space." The volume of the brain intracranial spaces is on average about 1700 ml in mature adults. The volume of the brain is approximately 1400 ml, and the volume of the intracranial blood is approximately 150 ml. The remaining 150 ml is filled with CSF (this volume may vary within 60 ml to 290 ml). The CSF circulates within the CSF space. CSF is formed principally by the choroid plexuses which secrete about 80% of the total volume of the CSF. The sources of the remainder are the vasculature of the subependymal regions and the pia matter. The total volume of the CSF is renewed several times per day, so that about 500 ml are produced every 24 hours (equivalent to about 20 ml/hr or 0.35 ml/min) in healthy adults. The production rate varies in the old and the young.

The cerebrospinal fluid is absorbed through the arachnoid villi, located principally over the superior surfaces of the cerebral hemispheres. Some villi also exist at the base of the brain and along the roots of the spinal nerves. The absorptive processes include bulk transport as well as diffusion across porous membranes. Substances present in the CSF can be cleared by such absorptive processes. Large molecules and cellular debris are also cleared by pinocytosis. The production and absorption of CSF are well

described in the medical literature. See, e.g., Adams et al. (1989) "Principles of Neurology," pp. 501-502.

Under a variety of circumstances, CSF may come to contain undesirable substances which can be harmful to a patient and/or foul implanted devices. For example, a number of diseases may be associated with toxic substances which are present in the CSF, such as Alzheimer's disease, Down's Syndrome, hereditary cerebral hemorrhage with amyloidosis of the Dutch-Type (HCHWA-D), epilepsy, narcolepsy, Parkinson's disease, polyneuropathies, multiple sclerosis, amyotrophic lateral sclerosis (ALS), myasthenia gravis, muscular dystrophy, dystrophy myotonic, other myotonic syndromes, polymyositis, dermatomyositis, brain tumors, Guillain-Barre-Syndrome, and the like.

In addition to such disease factors, the CSF may become contaminated with deleterious drugs, either because of a drug overdose or because of an accidental administration of a wrong drug. Additionally, tumor cells can be released into CSF naturally or as a result of surgery on brain tumors, and the like. The seeding of tumor cells into CSF circulation can place the patient at significant risk of metastatic tumor growth. In addition to such disease-related and drug substances, CSF can be contaminated by blood and high protein levels which can cause failure of the arachnoid villi and development of hydrocephalus. Such high blood and protein levels can also render the implantation of a ventricular shunt or a lumbar shunt problematic by occluding passages in the shunt intended to permit release of CSF to treat hydrocephalus and related conditions.

For all of these reasons, it would be desirable to provide methods, systems, and the like, for removing such deleterious substances from the CSF of a patient. Recently, a promising treatment for Alzheimer's disease has been proposed which relies on the removal of CSF from the CSF space using an implanted shunt. Usually, one end of the shunt will be implanted in a ventricle or elsewhere in the CSF space while the other end of the shunt will be implanted in the patient's abdomen or other suitable site for accepting continuous drainage of the CSF. By continuously draining the CSF at a relatively low rate, production of new CSF reduces the concentration of substances remaining in the endogenous CSF. While very promising, the use of internally implanted CSF shunts has certain drawbacks. For example, the amount by which the concentration of any contaminating substance may be lowered is limited by the relatively slow rate of CSF replacement. Therefore, the rate at which the concentration is lowered is relatively

slow, often taking a number of days to reach a new equilibrium. Such a slow process would often be ineffective for treating acute conditions, such as drug overdose or toxicity, the release of tumor cells following surgery, and the clearing of blood, proteins and other contaminating materials from CSF.

Thus, it would be desirable to provide improved and alternative methods, systems, and kits for removing substances from CSF for a variety of purposes. In particular, it would be desirable to provide such methods, systems, and kits which are able to reduce any concentration of such toxic and contaminating substances to very low levels and over very short time periods, typically less than 24 hours, preferably less than ten minutes. Such methods, systems, and kits should be safe, preferably employing conventional introduction techniques, and should have adequate safeguards to avoid excessive accumulation or depletion of CSF in the CSF space and to assure that the pressure within the patient's CSF space is not raised or lowered to an extent which would place the patient at risk. In addition to removing substances, it would be desirable to provide methods and systems for delivering therapeutic and other agents to the CSF, preferable to treat a condition associated with the substance being removed. It would further be desirable if the methods could be performed, in at least some instances, using only a single catheter or access device introduced to the patent. Such objectives will be met at least in part by the invention described hereinafter.

2. Description of the Background Art

Spiegel et al. (1981) N. Engl. J. Med 311:386-388, describe treatment of a methotrexate overdose by ventriculolumbar perfusion. Saline was introduced to a patient's right ventricle and CSF was removed using a lumbar needle. Lafolie et al. (1988) Medical Toxicology 3:248-252, describe the use of a lumbar needle to remove 5 ml volumes of CSF and return 5 ml volumes of saline.

U.S. Patent No. 4,686,085, describes a method for treating ischemic stroke by infusing an oxygenated mock CSF to a patient's cerebrospinal space and withdrawing CSF from a different location in the cerebrospinal space. U.S. Patent No. 5,683,357, shows bi-directional CSF flow through a shunt in a hydrocephalus patient. U.S. Patent No. 5,772,625, shows a hydrocephalus shunt without bi-directional flow. U.S. Patent Nos. 5,002,528 and 4,895,561, show dual lumen catheters for infusing and removing fluids from body cavities.

The treatment of Alzheimer's disease by removing cerebrospinal fluid from the CSF region of the brain is described in co-pending applications USSN 08/678,191, filed on July 11, 1996, and USSN 08/901,023, filed on July 25, 1997, both of which are assigned to the assignee of the present invention. The full disclosures of each of these two applications are incorporated herein by reference. The latter application is equivalent to WO 98/02202.

## SUMMARY OF THE INVENTION

The present invention provides improved and alternative methods and apparatus for removing and/or delivering substances to a patient's cerebrospinal fluid (CSF). In a first instance, the present invention provides for removing toxic and other contaminating substances from the CSF in a patient's CSF space. In a second instance, the present invention provides for delivering therapeutic and ameliorative agents to the CSF space, such as drugs, particularly chemotherapeutic drugs; biologicals, such as monoclonal antibodies; anesthetics; and the like. Often, the delivery and removal of the drugs or other active substances can be controlled to both provide rapid peaks and rapid removals, often permitting the use of higher concentrations and/or larger volumes of such substances than could be achieved by direct injection without the ability to remove the substance later. The methods and apparatus may be used for a variety of purposes including the treatment of diseases associated with the accumulation of toxic substances in the CSF, such as Alzheimer's disease, and the other diseases listed above. Additionally, the present invention will be useful for treating acute drug toxicity in the CSF space, typically resulting from overdose, accidental dosages, and the like, as well as removing residual amounts of drugs and anesthetics which have been properly administered to a patient but which are no longer necessary. The latter will be useful in reducing post-surgical and other recovery times. The present invention will still further be useful for removing toxic, immunogenic, neoplastic, and other deleterious substances which may be released into CSF circulation following surgery. In particular, the present invention may be used to remove tumor cells which may be released into CSF circulation following the surgical removal of a tumor from the brain or other location that can release cellular substances into the CSF. In addition, the present invention may find use in removing blood, proteins, and other contaminating substances which may be present in CSF prior to the implantation of a CSF drainage shunt or other surgical procedure in the

CSF space. The present invention is particularly advantageous since it can effectively reduce the concentrations of any of these substances to an arbitrarily low level. Moreover, the lowering of the concentration can be achieved in a relatively short period, typically less than 24 hours, often less than one hour, preferably less than 30 minutes, and more preferably less than ten minutes.

In a first aspect, methods according to the present invention for reducing the concentration of a toxic substance in a CSF space of a patient comprise identifying a patient having a condition related to the presence of a toxic substance in CSF and exchanging endogenous CSF for a substantially equal volume of a CSF replacement fluid. In this way, the concentration of the toxic substance is reduced. The identifying step may comprise identifying a patient having any of the diseases listed above, identifying a patient that has suffered a drug overdose or adverse drug reaction, or identifying a patient subject to the release of toxic substances in the CSF as a result of surgery, e.g., the release of tumor cells as the result of removal of a tumor. The methods will also find use in treating patients about to undergo a surgical procedure in the CSF space, typically implantation of a CSF drainage shunt of the treatment of hydrocephalus or any of the other CSF-related diseases listed above. These methods will all comprise identifying a patient about to undergo such a surgical procedure and thereafter exchanging endogenous CSF for substantially equal volume of the CSF replacement fluid in order to reduce the concentration of such substances in the CSF. Usually, the latter method will be employed to reduce the concentration of contaminating substances which can be toxic (as discussed above) and can also foul the CSF drainage shunt or interfere with other surgical procedures.

In a second aspect, a method according to the present invention for exchanging endogenous CSF in a CSF space of a patient with a CSF replacement fluid comprises implanting a single catheter so that a distal end of the catheter lies within the CSF space and a proximal end of the catheter lies outside of the patient. CSF replacement fluid is then infused through a first port on the distal end of the catheter into the CSF space. Endogenous CSF is removed through a second port on the distal end of the catheter from the CSF space. The ports are spaced-apart and optionally oriented in different directions to minimize removal of the freshly introduced CSF replacement fluid.

In a third aspect, a method according to the present invention for exchanging endogenous CSF in a CSF space of a patient with a CSF replacement fluid

comprises infusing the CSF replacement fluid by positive displacement into the CSF space. The endogenous CSF is removed, also by positive displacement from the CSF space.

In all three aspects of the methods, the replacement fluid may be infused simultaneously with the removal of the endogenous CSF. Usually, the replacement fluid will be infused at a rate which is substantially equal to the rate at which the endogenous CSF is removed in order to avoid any build up or depletion of fluid volume in the CSF space. Exemplary infusion rates for the CSF replacement fluid on the range from 0.1 ml/min to 50 ml/min, preferably from 1 ml/min to 15 ml/min, with the difference between infusion and removal rates never exceeding 10 ml/min, preferably never exceeding 1 ml/min, and more preferably being substantially equal.

Alternatively, in any of the three method aspects described above, the CSF replacement fluid may be infused sequentially with removing the endogenous CSF. Usually, the infusing and removing procedures will be performed alternatingly, but in some instances it may be possible that they will partially overlap. When only a single lumen having a single catheter is employed, however, infusion and removal through that lumen will have to be non-overlapping. With such sequential treatments, the volume of CSF replacement fluid infused and the volume of endogenous CSF removed at each cycle will usually be equal, typically being in the range from 10 ml to 200 ml, usually from 25 ml to 100 ml.

In all cases, including both simultaneous and sequential infusion and removal, the total volume of CSF replacement fluid infused and endogenous CSF removed will usually be in the range from 50 ml to 2000 ml, more usually from 50 ml to 500 ml, and preferably from 50 ml to 150 ml. The total volume will usually be removed over a relatively short period of time, typically from ten minutes to 24 hours, usually from ten minutes to two hours. In order to avoid injury to the patient, it is desirable that the volume of CSF replacement fluid infused be maintained relatively closely to the volume of endogenous CSF being removed at any given time, as described above. For simultaneous infusion and removal, this can be achieved by controlling the infusion and removal rates to the same levels. In this way, the total amount of "CSF" (including both endogenous CSF and CSF replacement fluid) present in the CSF space will remain generally unchanged. In the case of sequential infusion and removal, the total amount of "CSF" present will vary slightly depending on the amount of fluid most recently infused

and/or removed. By maintaining the discrete volumes being introduced and removed to relatively low levels, as set forth above, the total amount of CSF present in the CSF space will never vary to a potentially harmful extent.

In all cases, the difference between removed and infused volumes may be summed (totalized) over time to assure that there is no significant accumulation or depletion of total CSF present in the CSF space. Additionally, it may be desirable to weigh or otherwise keep track of the CSF replacement fluid which has been introduced (e.g., by monitoring the reduction in weight of the CSF replacement fluid source) and the amount of endogenous CSF removed (by monitoring the amount of fluid accumulating in the waste receptacle) in order to further assure that the fluid balance is being maintained properly.

The CSF replacement fluid will be infused to a pre-selected infusion location within the patient's CSF space and the endogenous CSF will be removed from a pre-selected removal location in the patient's CSF space. The CSF space has been defined above, and the infusion location and the removal location are preferably spaced-apart by distance of at least 0.5 cm, preferably at least 4 cm, in order to assure that the CSF replacement fluid being infused will not flow directly into the removal location so that it is removed before it has a chance to mix with and dilute the endogenous CSF. The phrase "endogenous CSF" is meant to include both the native CSF which is produced and secreted by the patient into the CSF space as well as any portion of the CSF replacement fluid which becomes mixed with the native CSF. While it will be desirable to the extent possible to avoid mixing and removal of the CSF replacement fluid, it will be appreciated that some mixing is inevitable and that removal of the CSF replacement fluid together with the native CSF will occur, particularly during latter stages of the treatment protocol. The removal of the CSF replacement fluid can be minimized, however, by spacing the removal location as far as possible from the infusion location, as discussed below. In the simplest embodiments of the present invention, however, the infusion and removal can be performed through a single lumen of a single catheter so that the infusion location and removal location are in fact at the same place. Although this may be less efficient than other techniques described herein, it remains a viable approach for performing the methods of the present invention.

The infusion and removal locations may be virtually any portion of the CSF space, usually being within a ventricle, a cisterna magna, or a subarachnoid space.

When using a single catheter with either a common or multiple spaced-apart infusion/removal ports, the infusion and removal locations will usually be in the same region of the CSF space, typically being in a ventricle, most typically being in a lateral ventricle. When separate catheters having separate infusion and removal ports are employed, the infusion location and removal location may be present virtually anywhere in the CSF space, with exemplary infusion locations being in a lateral ventricle and a lumbar location (e.g., L3 to L5) and exemplary removal locations being in the cisterna magna, the lumbar region, and the like.

In all of the above methods, the CSF replacement fluid may be any sterile, physiologically compatible liquid which may be infused into the CSF space to temporarily replace the native or endogenous CSF as new endogenous CSF is produced and recirculated. Suitable CSF replacement fluids include commercially available neurological irrigation fluids, such as Physiosol® fluid (Abbott Laboratories), as described in the medical literature.

The present invention further provides systems for exchanging endogenous CSF in a CSF space of a patient with a CSF replacement fluid. In a first aspect, a system according to the present invention comprises a source of CSF replacement fluid, a catheter having a proximal end, a distal end, and at least one lumen extending from near the distal end to near the proximal end, and first and second positive displacement liquid transfer devices. The first positive displacement liquid transfer device, such as a syringe, peristaltic pump, piston pump, or the like, is connected between a proximal end of the catheter lumen and the CSF replacement fluid source to deliver CSF replacement fluid through the lumen. The second positive displacement liquid transfer device, which can also be a syringe, a peristaltic pump, or a piston pump, is connected to the proximal end of the catheter lumen to remove endogenous CSF through that lumen. This system is particularly suited for performing sequential infusion and removal operations where the first positive displacement liquid transfer device infuses the CSF replacement fluid through the single (common) lumen of the catheter while the second positive displacement liquid transfer device removes the endogenous CSF (typically, partially mixed with the CSF replacement fluid) through the same lumen.

In a second aspect, systems according to the present invention comprise a source of CSF replacement fluid, a first catheter, and a second catheter, where both catheters have a proximal end, a distal end, and a least one lumen extending from near the

distal end to near the proximal end. The system further includes a first positive displacement liquid transfer device, which can be any of the devices listed above, connected between the proximal end of the first catheter lumen and the CSF replacement fluid source to deliver CSF replacement fluid through the lumen to the CSF space. A second positive displacement liquid transfer device, which can also be any of the devices disclosed above, is connected to the proximal end of the second catheter lumen to remove endogenous CSF through that lumen. The second system is particularly suited for simultaneous infusion and removal of CSF from the CSF space where the distal ends of the first and second catheters are located at different positions within the CSF space. Since the first and second catheters are separate, they may be located at quite different locations, e.g., the first catheter may be in the lateral ventricle while the second catheter may be in a different ventricle, at the cisterna magna, or within the lumbar region of the subarachnoid space.

In a third aspect, systems according to the present invention comprise a source of CSF replacement fluid and a single catheter having a proximal end, a distal end, and at least two isolated lumens extending from near the proximal end to near the distal end. A first of the isolated lumens terminates at a first port near the distal end, and a second of the isolated lumen terminates at a second port near the distal end. The first and second ports are spaced-apart by a distance of at least 0.5 cm, preferably at least 1 cm, and more preferably at least 4 cm. The system may optionally comprise first and second positive displacement liquid transfer devices, or may comprise centrifugal pumps, or other non-positive displacement liquid transfer devices which may be controlled to provide desired infusion and/or removal volumes. These systems are particularly suitable for placement within a ventricle or other single location within the CSF space where the CSF replacement fluid may be infused at a location spaced-apart from the location from which it is withdrawn.

In all of the above systems, the first and second positive displacement liquid transfer devices will preferably be coordinated so that the volumes of CSF replacement fluid infused will be substantially equal to the volumes of endogenous CSF removed. The coordination can be mechanical, e.g., the first and second positive displacement liquid transfer devices may be mechanically linked. Alternatively, the amounts of CSF replacement fluid delivered and amounts of endogenous CSF removed may be monitored by conventional liquid flow monitoring devices. Based on the

measured amounts or flow rates, the transfer devices can be controlled in order to equalize the volumes of fluid being delivered and removed. All the systems will preferably further comprise safety devices for stopping operation of the system in the event of over pressure, under pressure, or other dangerous operating conditions. The typical over pressure value at which the system will be shut down is 5 cm $H_20$ over nominal measured ICP (intracranial pressure), while a typical under pressure value will be 5 cm $H_20$ under nominal measured ICP, preferably 5 cm $H_20$ under.

The present invention still further provides a cerebral fluid exchange catheter comprising a catheter body having a proximal end and a distal end. An inflatable balloon is mounted at or near the distal end of the catheter body, and a lumen or other inflation tube or member is provided in or over the catheter body to permit selective inflation of the balloon when present in a ventricle or other body lumen. At least one additional lumen or fluid delivery tube is also provided as part of the catheter to permit delivery of a fluid, typically a CSF replacement fluid, to a region outside of the balloon. The catheter is typically used by introducing its distal end including the balloon into a ventricle or other body lumen. The balloon is then inflated with a suitable inflation medium, typically physiological saline, mock CSF, radiopaque dye, or other incompressible fluid, and the CSF in the ventricle is displaced. Optionally, an additional lumen in the catheter can be used for removing the displaced fluid, further optionally by the application of a negative pressure through said additional lumen. Alternatively, the fluid can be simply displaced to other regions of the CSF space and/or withdrawn through a separate CSF removal catheter. After the balloon has been fully inflated to displace a selected volume of CSF, typically in the range from 1 ml to 20 ml, preferably from 1 ml to 10 ml, the balloon will be deflated, and a volume of CSF replacement fluid introduced, typically simultaneously with the balloon deflation. Preferably, the balloons will be non-distensible so that they will inflate to predetermined volumes, not dependent on inflation pressure. Particular balloon styles may then be selected for an individual patient based on pre-operative imaging of the target ventricle. Usually, the CSF replacement fluid will be introduced through a separate, isolated lumen within the catheter body, where the lumen has a port which lies adjacent to the balloon. Alternatively, it will be possible to use the CSF replacement fluid to inflate the balloon and thereafter release the fluid from the balloon to both deflate the balloon and provide the desired volume of CSF replacement fluid to the ventricle.

The present invention still further provides kits for performing any of the methods described above. The kits will include at least one implantable catheter having a proximal end, a distal end, and a lumen therethrough. In addition to the catheter, the kits will include instructions for use setting forth any of the methods described above. The kits may further comprise packaging for holding the catheter together with the instructions for use, wherein usually at least the catheter is maintained sterilely within the package. The kits may still further comprise a second implantable catheter having a proximal end, a distal end, and a lumen therethrough. The kits may even further comprise a source of the CSF replacement fluid. Moreover, any of the systems described above may be provided in kit form where any or all of the kit components may be maintained sterilely within appropriate packages and wherein appropriate instructions for use are provided.

## BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 illustrates the portions of the cranium and vertebral column which are encased within the meninges in which comprise the "CSF space" of the present invention. Specific regions within the CSF space are identified.

Fig. 2 is a schematic illustration of a first exemplary system according to the present invention for treating a patient.

Figs. 3 and 3A illustrate a catheter used in the system of Fig. 2.

Figs. 4A and 4B illustrate alternative fluid control units for the system of Fig. 2.

Fig. 5 illustrates a second exemplary system according to the present invention.

Fig. 6 illustrates a third exemplary system constructed in accordance with the principles of the present invention.

Figs. 7, 7A, and 7B illustrate a catheter which could be used in the methods of the present invention.

Figs. 8A and 8B illustrate flow control mechanisms that can be used in the systems of Figs. 5 and 6.

Fig. 9 illustrates a kit constructed in accordance with the principles of the present invention.

Figs. 10A - 10D illustrate use of the catheter of Figs. 7, 7A, and 7B in performing methods according to the present invention.

## DESCRIPTION OF THE SPECIFIC EMBODIMENTS

Referring now to Figs. 2, 3, and 3A, a system 10 for exchanging endogenous cerebrospinal fluid in a CSF space patient P will be described. The system comprises a catheter 12 having a single lumen 14 and a plurality of infusion/aspiration ports 16 near its distal end. The catheter has a connecting hub 18 at its proximal end, and the connecting hub 18 is connected to a flow control mechanism 20 which is described in more detail hereinafter. Catheter 12 may optionally include a stylet 19 which can be placed in the lumen 14 of the catheter to stiffen the lumen and facilitate introduction to the CSF space of the patient. The flow control mechanism 20 will receive a CSF replacement fluid from a source 22 and selectively deliver that replacement fluid to the catheter 12 so that it may be infused into a CSF space. The flow control mechanism 20 will also receive endogenous CSF from the catheter 12 and direct the endogenous CSF to a waste disposal location 24. The CSF replacement fluid source 22 may be a bag or other sterile receptacle for holding any of the liquids described earlier, while the waste receptacle 24 may be a bag, bottle, or other conventional medical liquid waste receptacle.

The flow control mechanism 20 may comprise any conventional liquid flow management apparatus capable of selectively delivering the CSF replacement fluid to the catheter and for selectively removing the endogenous CSF from the catheter. For example, as illustrated in Fig. 4A, the mechanism 20 may comprise an infusion syringe 30 which contains the CSF replacement fluid and is able to deliver the fluid through a three-way connector or valve 32 into the proximal connecting hub 18. The mechanism 20 will also include a removal syringe 40 which is able to apply a vacuum to the connecting hub 18 to withdraw endogenous CSF fluid from the catheter 12. As illustrated in Fig. 4A, the CSF replacement fluid could be introduced as a bolus into the CSF space, allowed to mix for a short period of time, and thereafter withdrawn using the removal syringe 40. It will be appreciated that a significant portion of the CSF replacement fluid might be removed together with the endogenous CSF, thus reducing the effectiveness of the system. The flow control mechanism 20 at Fig. 4A could be improved by connecting both the infusion syringe 30 and removal syringe 40 to a larger volume source of CSF replacement fluid and a larger receptacle, respectively. That way,

the syringes could be used to alternatively pump and withdraw volumes of CSF from the CSF space in order to incrementally exchange the endogenous CSF for the CSF replacement fluid. Optionally, a pressure gauge 34 could be placed on the common inlet/outlet line to permit monitoring of the infusion removal pressures.

Referring now to Fig. 4B, an alternative mechanism for sequentially delivering CSF replacement fluid and withdrawing endogenous CSF is illustrated. CSF source 22 and waste receptacle 24 are connected to an alternative flow control mechanism 20'. A one-way valve 50 permits the CSF replacement fluid to be drawn into infusion syringe 52 when the actuator handle 54 is moved in a rightward direction. As the infusion syringe 52 is filling with replacement fluid, a removal syringe 54 is drawing endogenous CSF from the catheter 12 through another one-way valve 58. After filling both syringes 52 and 56, the replacement fluid can be delivered to the catheter 12 by reversing the direction of actuator 54 to move in a leftward direction. This motion expels the CSF replacement fluid from syringe 52 through one-way valve 60 into the catheter. The endogenous CSF in syringe 56 will be directed to the waste receptacle 24 by one-way valves 58 and 62. In this way a series of sequential pulses or small volumes of the CSF may be delivered to the patient while equal volumes of the endogenous CSF are removed from the patient.

Referring now to Fig. 5, a second system 100 comprising a catheter 102 having spaced-apart ports 104 and 106 near its distal end and a proximal connector 108 at its proximal end is illustrated. The system 100 further includes a CSF replacement fluid source 110 and an endogenous CSF waste receptacle 112. In addition, the system 100 includes a flow control mechanism 114 for controlling the flow of the CSF replacement fluid from the source 110 to port 104 and further controlling the flow of endogenous CSF fluid from port 106 to the waste receptacle 112. Catheter 102 will include at least two isolated lumens, one from each of the ports 104 and 106 to separate connections of the connector 108. Exemplary flow control mechanisms will be described below.

A third system 200 (Fig. 6) according to the present invention includes a first catheter 202 having a distal end 204 with at least one infusion port thereon and a proximal connector 206. A second catheter 208 has a distal end 210 with at least one aspiration port and a proximal connector 212. The proximal connector 206 of infusion catheter 202 and the proximal connector 212 of aspiration catheter 208 are both connected to flow control mechanism 220 which will be described in more detail below.

The flow control mechanism 220 receives a CSF replacement fluid from a CSF replacement fluid source 222 and directs endogenous CSF from aspiration catheter 208 to a waste receptacle 224.

Referring now to Figs. 7, 7A, and 7B, an exemplary catheter 400 comprises a catheter body 402 having a distal end 404 and a proximal end 406. A balloon 410 (or other inflatable displacement member) is positioned at or near the distal end 404 of the catheter body 402, and a hub 412 is secured to the proximal end 406 of the catheter body. In the illustrated embodiment, the catheter body 402 comprises three fluidly isolated lumens 420, 422, and 424 (as best seen in Figs. 10A and 10B). Lumen 420 is connected to an inflation connector 430 in hub 412 and terminates in an inflation port 432 within the balloon 410. The second lumen 422 is connected to an aspiration connector 434 which terminates at an aspiration port 436 located immediately distal of the balloon 410. The third lumen 424 is connected to an infusion connector 438 on the hub 412 and terminates in an infusion port 440 at the distal tip of the catheter. In this way, a suitable inflation medium, such as saline or other incompressible fluid, may be introduced through the connector 430 and into the balloon 410. The same port and lumen may also be used to deflate the balloon. The aspiration connector 434 may be connected to a suitable vacuum or reduced pressure source in order to aspirate CSF or other fluid through the port 436 from the ventricle or other body structure. Finally, the CSF or other replacement fluid may be introduced through the infusion connector 438 and into the ventricle through the infusion port 440.

Use of the catheter 400 for performing CSF removal and replacement is illustrated in Figs. 10A - 10D. Initially, the distal end of the catheter 400, including balloon 410 in its deflated configuration is introduced to a brain ventricle BV in a conventional manner, typically through a sheath S. After being properly positioned in the brain ventricle, as may be confirmed by fluoroscopic imaging, the balloon 410 may be inflated, as shown in Fig. 10B. Inflation of the balloon directly displaces CSF from the brain ventricle. While displacement may result in fluid transport to other portions of the CSF space, it will be preferred that the displaced CSF be collected through the aspiration port 436, as illustrated. Optionally, a slight negative pressure, typically in the range from 1 cm $H_20$ to 10 cm $H_20$, may be applied to assist in CSF removal. After the balloon 410 is fully inflated, as illustrated in Fig. 10C, the CSF displacement will cease. Note that the balloon 410 may be formed from a distensible or non-distensible material, preferably

being non-distensible having a fixed, inflated volume in the range from 0.1 ml to 10 ml. The inflation pressures will usually be moderate as described below.

After the displacement has been completed, the balloon 410 will be deflated, permitting introduction of the CSF replacement fluid. The exemplary embodiment, CSF replacement fluid will be introduced through the distal port 440, as illustrated in Fig 10D. After the full volume of replacement fluid has been introduced, which will typically be equal to the volume of endogenous CSF removed, the catheter may be used for further introduction of CSF replacement fluid, optionally in combination with a separate removal catheter, as described elsewhere in this application. Alternatively, the balloon may be repeatedly inflated and deflated in order to introduce the CSF replacement fluid over time. Such repeat procedures may be performed at selected intervals, which may range from hours to days.

Referring now to Figs. 8A and 8B, alternative flow control mechanisms 114 and 220 (Figs. 5 and 6, respectively) will be illustrated. Both these flow control mechanisms will work either with a single catheter having dual ports or dual catheters having single (or multiple) ports. Both will also provide for simultaneous delivery of CSF replacement fluid in aspiration of endogenous CSF. The simplest flow control mechanism is illustrated in Fig. 8A where CSF fluid source 400 may be suspended above a flow control mechanism 402 having a one-way valve 404 in line with the fluid outlet line 406. Fluid from the source 400 will flow through the line 406, through the one-way valve 404, and to the delivery catheter 102 or 202. The fluid will thus infuse into the target region of the CSF space based on the gravity head, typically 1 cm $H_20$ to 10 cm $H_20$ above measured intracranial pressure. Infusion of the CSF replacement fluid into the CSF space, in turn, will displace fluid into the catheter 102 or 202 and back through a line 410, through a one-way valve 412, and into a waste receptacle 420. The one-way valves 404 and 412 are provided to assure that material from the catheter does not flow retrograde into the CSF replacement fluid source 400 and that waste CSF from receptacle 420 does not flow retrograde back into the patient. System of Fig. 8A is advantageous in that it operates solely on hydrostatic pressures induced by gravity. Pressure to the patient can be limited by locating the source 400 and appropriate height above the patient and the aspiration of an equivalent amount of endogenous CSF (to that of the CSF replacement fluid) will usually result from the equal volume displacement of the endogenous CSF from the CSF space into the aspiration port.

The delivery of CSF replacement fluid and aspiration of endogenous CSF can be controlled by a more complex system which permits closer monitoring and control of the treatment parameters. As illustrated in Fig. 8B, a flow control mechanism 500 may comprise a pair of fluid transfer devices, typically positive displacement fluid transfer devices 502 and 504. A controller 506, which may be a digital controller, a digital computer, an analog controller, or other conventional electronic control system, will be connected to the flow control mechanism 500 to monitor and control flows therethrough. Usually, the controller 506 will control operation of both the infusion transfer device 502 and aspiration transfer device 504, typically electric pumps, more typically electric positive displacement pumps, such as peristaltic pumps. Flow of CSF replacement fluid from a fluid source 510 will pass through the transfer device 502 to an output line 512 which will then pass to the infusion lumen of catheter 102 or 202. Endogenous CSF from the aspiration lumen of catheter 102 or 203 will pass inwardly through line 520 to the second liquid transfer device 504 to a waste receptacle 530. Control of both the infusion flow rates and aspiration flow rates may be accomplished by controlling the pump speeds, particularly in the case of positive displacement pumps, or by measuring the flows using flow measurement elements 540 and 542 placed in line in the infusion line 512 and aspiration line 520, respectively. Optionally, the flow control may be controlled through the positive displacement transfer devices 502 and 504 and additionally monitored using appropriate measurement systems to provide a further measure of safety that the amounts of CSF replacement fluid being delivered are equal to the amounts of endogenous CSF being removed. In addition to monitoring flow rates, it will usually be desirable to also monitor infusion pressures and/or aspiration pressures to make sure that pressures outside of the safe range are not being created within the CSF space. Although a number of specific systems for delivering and controlling the infusion and aspiration of CSF from a patient's CSF space have been illustrated, it will be appreciated that a wide variety of systems can be implemented for practicing the inventions of the present.

One additional system which is not illustrated would utilize a pair of synchronized syringes, one coupled to an infusion lumen and the other coupled to a removal lumen. The syringes would by driven simultaneously, but out-of-phase, so that one syringe would deliver fluid while the other would withdraw fluid.

In addition to the methods and systems described above, the present invention will further comprise kits comprising one or more system components together

with instructions for use setting forth any of the above methods. As illustrated in Fig. 9, a kit may comprise at least one implantable catheter 700, usually also comprising at least a second implantable catheter 702 combination with instructions for use (IFU). The catheters 700 and 702 together with the instructions for use with typically be packaged in a conventional medical device package 704, such as a pouch, tube, tray, box, or the like. In addition to the catheter(s) and instructions for use, the kits may further comprise other components of the systems described above, such as the flow control mechanisms, the CSF replacement fluid sources, and/or the endogenous CSF waste receptacles. These components are shown schematically as 710 in Fig. 9.

While the above is a complete description of the preferred embodiments of the invention, various alternatives, modifications, and equivalents may be used. Therefore, the above description should not be taken as limiting the scope of the invention which is defined by the appended claims.

WHAT IS CLAIMED IS:

1. A system for exchanging endogenous cerebrospinal fluid in a CSF space of a patient with a CSF replacement fluid, said system comprising;

a source of CSF replacement fluid;

a catheter having a proximal end, a distal end, and at least one lumen extending from near the distal end to near the proximal end;

a first positive displacement liquid transfer device connected between a proximal end of the catheter lumen and the CSF replacement fluid source to deliver CSF replacement fluid through the lumen; and

a second positive displacement liquid transfer device connected to a proximal end of the catheter lumen to remove endogenous CSF through the lumen.

2. A system for exchanging endogenous CSF fluid in a CSF space of a patient with a CSF replacement fluid, said system comprising:

a source of CSF replacement fluid;

a first catheter having a proximal end, a distal end, and at least one lumen extending from near the distal end to near the proximal end;

a second catheter having a proximal end, a distal end, and at least one lumen extending from near the distal end to near the proximal end;

a first positive displacement liquid transfer device connected between a proximal end of the first catheter lumen and the CSF replacement fluid source to deliver CSF replacement fluid through the lumen; and

a second positive displacement liquid transfer device connected to a proximal end of the second catheter lumen to remove endogenous CSF through the lumen.

3. A system for exchanging endogenous cerebrospinal fluid (CSF) in a CSF space of a patient with a CSF replacement fluid, said system comprising:

a source of CSF replacement fluid; and

a catheter having a proximal end, a distal end, and at least two isolated lumens extending from near the proximal end to near the distal end, wherein the first lumen terminates at a first port near the distal end and the second lumen terminates at a

second port near the distal end, and wherein the first and second ports are spaced-apart by a distance of at least 0.5 cm.

4. A system as in claim 3, further comprising a positive displacement liquid transfer device connected between the CSF replacement fluid source and the proximal end of the first lumen to deliver CSF replacement fluid to the first port.

5. A system as in claim 4, further comprising a second positive displacement liquid transfer device connected to the proximal end of the second lumen to remove fluid from the second port.

6. A system as in any of claims 1, 2, and 5, wherein the first and second positive displacement liquid transfer devices are mechanically linked to equalize the volumes of fluid being delivered and removed.

7. A system as in any of claims 1, 2, and 5, further comprising means for monitoring the amounts of CSF replacement fluid being delivered and endogenous CSF being removed.

8. A system as in claim 7, further comprising means for controlling the first and second positive displacement devices to equalize the volumes of fluid being delivered and removed.

9. A system as in any of claims 1, 2, and 5, wherein the positive displacement devices comprise reciprocating pistons.

10. A system as in claim 9, wherein the reciprocating pistons are part of syringe devices.

11. A system as in claim 9, wherein the positive displacement devices comprise peristaltic pumps.

12. A system as in any of claims 1, 2, and 5, further comprising means for stopping the system if a pressure of the replacement CSF delivered to the catheter lumen exceeds a safe level.

13. A system as in claim 12, wherein the safe level is 10 cm $H_20$ over initial intracranial pressure.

14. A system as in any of claims 1, 2, and 5, further comprising means for stopping the system if measured intracranial pressure falls below a safe level.

15. A system as in claim 14, wherein the safe level is 10 cm $H_20$ below the measured intracranial pressure.

16. A cerebral fluid exchange catheter comprising:
a catheter body having a proximal end and a distal end;
an inflatable balloon near the distal end;
means for inflating and deflating the balloon; and
means for delivering a fluid to a region outside the balloon as the balloon is deflated.

17. A cerebral fluid exchange catheter as in claim 16, wherein the inflator means comprises a lumen in the catheter body that delivers inflation medium to an interior of the balloon.

18. A cerebral fluid exchange catheter as in claim 17, wherein the delivering means comprises a second lumen in the catheter body that releases fluid through a port adjacent to the balloon.

19. A method for reducing the concentration of a toxic substance in cerebrospinal fluid (CSF) in a CSF space of a patient, said method comprising:
identifying a patient having a condition related to the presence of a toxic substance in the patient's CSF;
removing endogenous CSF; and
simultaneously infusing a substantially equal volume of a CSF replacement fluid, wherein the concentration of the toxic substance is reduced.

20. A method as in claim 19, wherein identifying a patient comprises identifying a patient having a disease selected from the group consisting of Alzheimer's disease, Down's Syndrome, hereditary cerebral hemorrhage with amyloidosis of the Dutch-Type (HCHWA-D), epilepsy, narcolepsy, Parkinson's disease, polyneuropathies, multiple sclerosis, amyotrophic lateral sclerosis (ALS), myasthenia gravis, muscular

dystrophy, dystrophy myotonic, other myotonic syndromes, polymyositis, dermatomyositis, brain tumors, Guillain-Barre-Syndrome, and the like.

21. A method as in claim 19, wherein identifying a patient comprises identifying a patient that has suffered a drug overdose or adverse drug reaction.

22. A method as in claim 19, wherein identifying a patient comprises identifying a patient subject to the release of toxic substances into the CSF as a result of surgery.

23. A method as in claim 22, wherein the toxic substances are tumor cells.

24. A method as in claim 19, wherein the toxic substance is blood in the CSF.

25. A method as in claim 19, wherein the toxic substance is excess protein in the CSF.

26. A method for removing substances from cerebrospinal fluid (CSF) in a CSF space of a patient who will undergo a surgical procedure in the CSF space, said method comprising:

identifying a patient who will undergo a surgical procedure on a CSF space; and

exchanging endogenous CSF for a substantially equal volume of a CSF replacement fluid, wherein the concentration of the substances is reduced.

27. A method for exchanging endogenous cerebrospinal fluid (CSF) in a CSF space of a patient with a CSF replacement fluid, said method comprising:

implanting a single catheter so that a distal end of the catheter lies within the CSF space and a proximal end of the catheter remains outside of the patient;

infusing the CSF replacement fluid through a first port on the distal end of the catheter into the CSF space; and

removing endogenous CSF through a second port on the distal end of the catheter from the CSF space, wherein the first and second ports are spaced-apart by a distance of at least 0.5 cm.

28. A method for exchanging endogenous cerebrospinal fluid (CSF) in a CSF space of a patient with a CSF replacement fluid, said method comprising:

infusing the CSF replacement fluid by positive displacement into the CSF space; and

removing the endogenous CSF by positive displacement from the CSF space.

29. A method as in claim 26, which exchanging endogenous CSF for a replacement fluid comprises simultaneously infusing the CSF replacement fluid and removing the endogenous CSF.

30. A method as in any of claims 19 to 22, and 27 to 29, wherein the CSF replacement fluid is infused at a rate which is substantially equal to the rate at which the endogenous CSF is removed.

31. A method as in claim 28, wherein the CSF replacement fluid is infused at a rate in the range from 0.1 ml/min to 50 ml/min with the difference between infusion rate and removal rate never exceeding 10 ml/min.

32. A method as in claim 28, wherein the CSF replacement fluid is actively infused at an infusion pressure and wherein the endogenous CSF is actively removed by applying a negative pressure.

33. A method as in claim 30, wherein the endogenous CSF is actively removed by applying a negative pressure and the CSF replacement fluid is passively infused.

34. A method as in any of claims 27 to 29, wherein exchanging endogenous CSF for a replacement fluid comprises infusing the CSF replacement fluid sequentially with removing the endogenous CSF.

35. A method as in claim 34, wherein the infusing and removing are performed alternatingly.

36. A method as in claim 35, wherein volumes of CSF replacement fluid in the range from 1 ml to 10 ml are infused alternatingly with the removal of equal volumes of endogenous CSF.

37. A method as in any of claims 19 to 22, and 27 to 29, wherein the total volumes of CSF replacement fluid infused and endogenous CSF removed are in the range from 50 ml to 2000 ml.

38. A method as in claim 37, wherein the total volume of CSF replacement fluid infused is substantially equal to the total volume of endogenous CSF removed.

39. A method as in claims 19 to 22, and 27 to 29, wherein the CSF replacement fluid is infused to an infusion location in the CSF space and wherein the endogenous CSF is removed from a removal location in the CSF space.

40. A method as in claim 39, wherein the infusion location and the removal location are spaced-apart by a distance of at least 0.5 cm.

41. A method as in claim 39, wherein the infusion location is within a ventricle, a cisterna magna, or a subarachnoid space.

42. A method as in claim 39, wherein the removal location is within a ventricle, a cisterna magna, or a subarachnoid space.

43. A method as in any of claims 19 to 29, wherein the CSF replacement fluid is a neurosurgical replacement fluid.

44. A method as in claim 27, wherein the infusing of the CSF replacement fluid and the removing of the endogenous CSF are performed simultaneously.

45. A method as in claim 27, wherein the infusing of the CSF replacement fluid and the removing of the endogenous CSF are performed sequentially.

46. A method as in any of one of the claims 44 and 45, wherein the infusing and removing are performed through different ports which are fluidly isolated from each other.

47. A method as in claim 28, wherein infusing the CSF replacement fluid by positive displacement comprises injection using a syringe or pumping using a peristaltic or piston pump.

48. A method as in claim 28, wherein removing the endogenous CSF by positive displacement comprises aspiration using a syringe or pumping using a peristaltic or piston pump.

49. A method for delivering a fluid to a brain ventricle;

inflating a balloon within the ventricle to displace fluid from the ventricle; and

delivering a CSF replacement fluid to the ventricle as the balloon is deflated.

50. A method as in claim 49, further comprising removing endogenous CSF from the ventricle as the balloon is inflated.

51. A method as in claim 49, where the delivering and replacing steps are performed through isolated lumens in a single catheter.

52. A method as in claim 51, wherein the balloon is inflated and deflated through a third lumen in the same catheter.

53. A method as in claim 49, further comprising transcutaneously positioning the catheter so that the balloon lies within the ventricle prior to the inflating and delivering steps.

54. A method as in claim 49, wherein the balloon is inflated with CSF replacement fluid and the delivering step comprises releasing the replacement fluid from the balloon.

55. A kit comprising:

at least one implantable catheter having a proximal end, a distal end, and a lumen therethrough; and

instructions for use setting forth a method according to any of claims 19 to 28, and 47.

56. A kit as in claim 55, further comprising packaging for holding the catheter together with the instructions for use, wherein at least the catheter is sterile within the package.

57. A kit as in claim 56, further comprising a second implantable catheter having a proximal end, a distal end, and a lumen therethrough.

58. A kit as in claim 57, further comprising a source of a CSF replacement fluid.

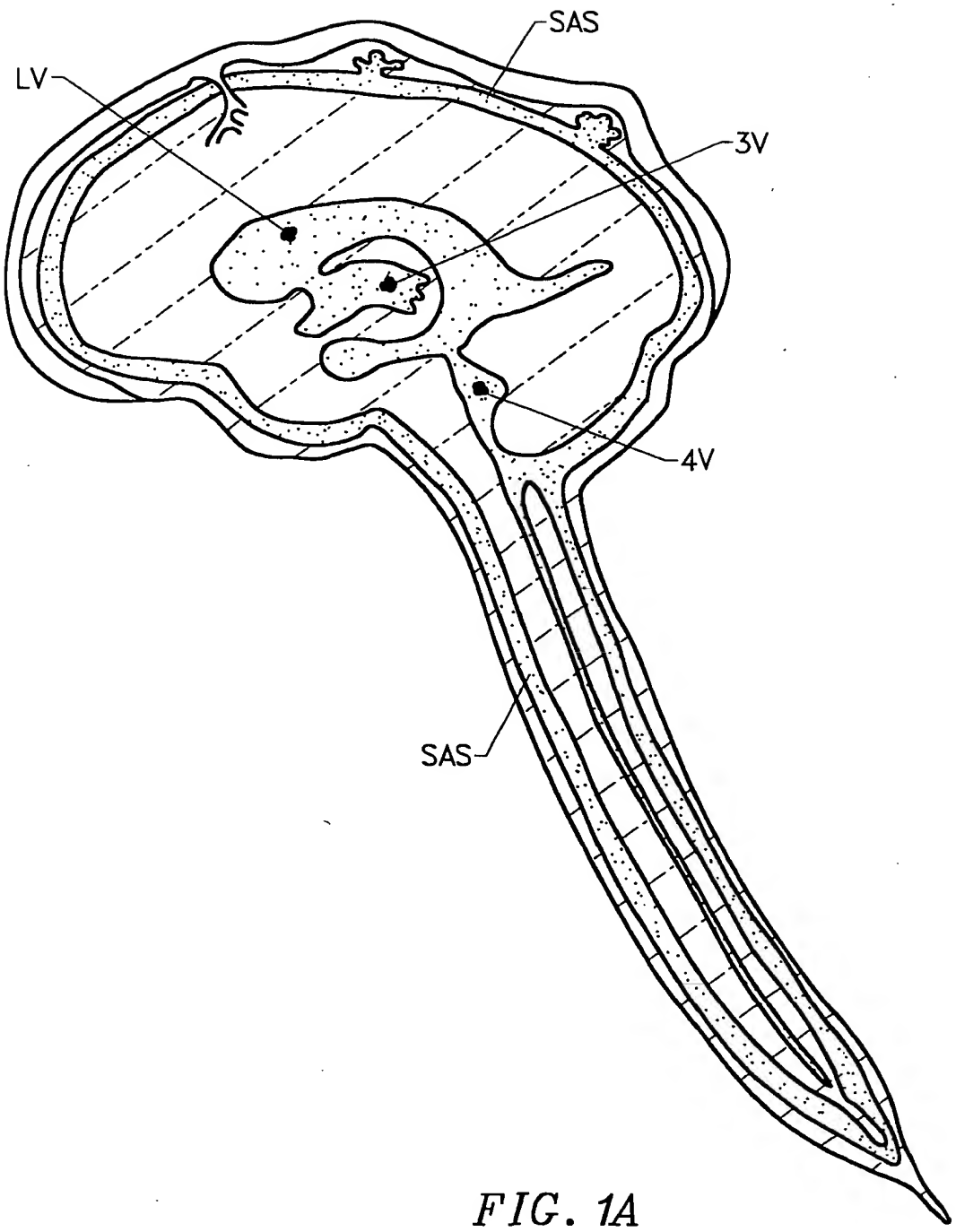


FIG. 1A

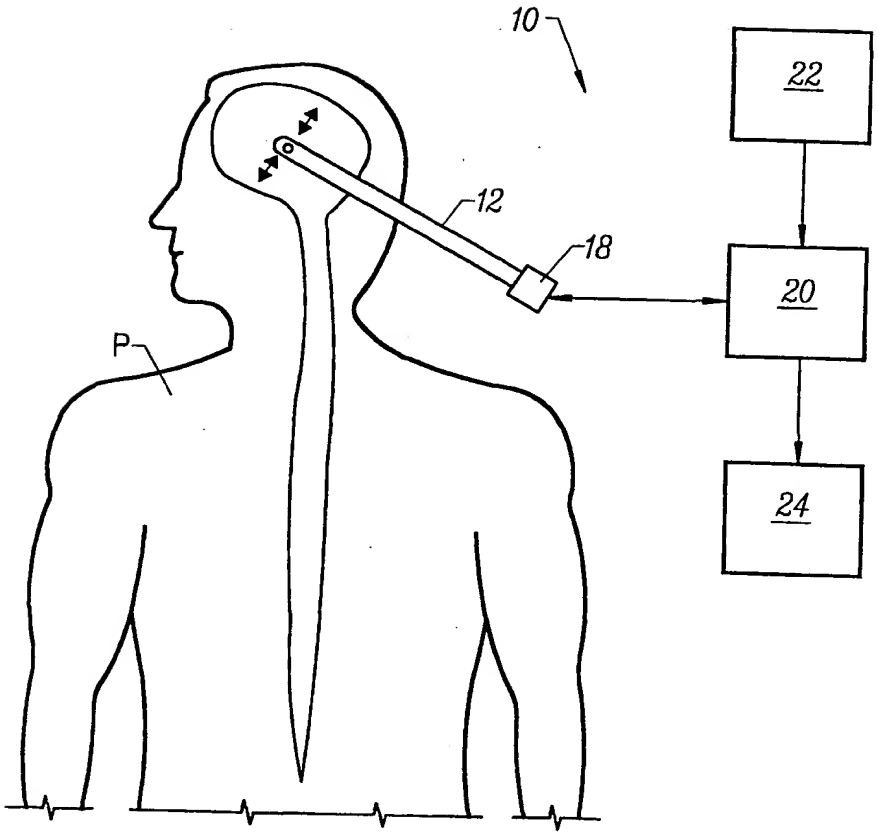


FIG. 2

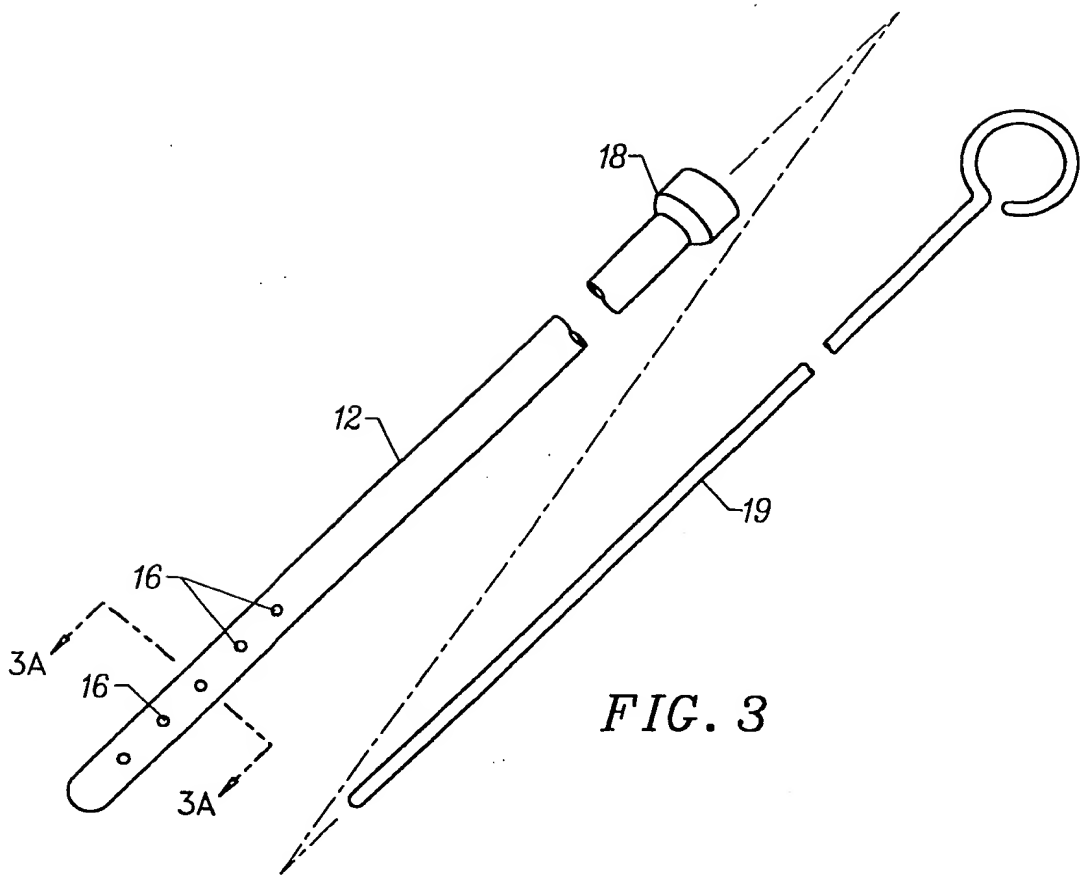


FIG. 3

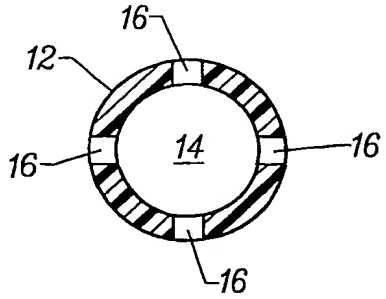


FIG. 3A

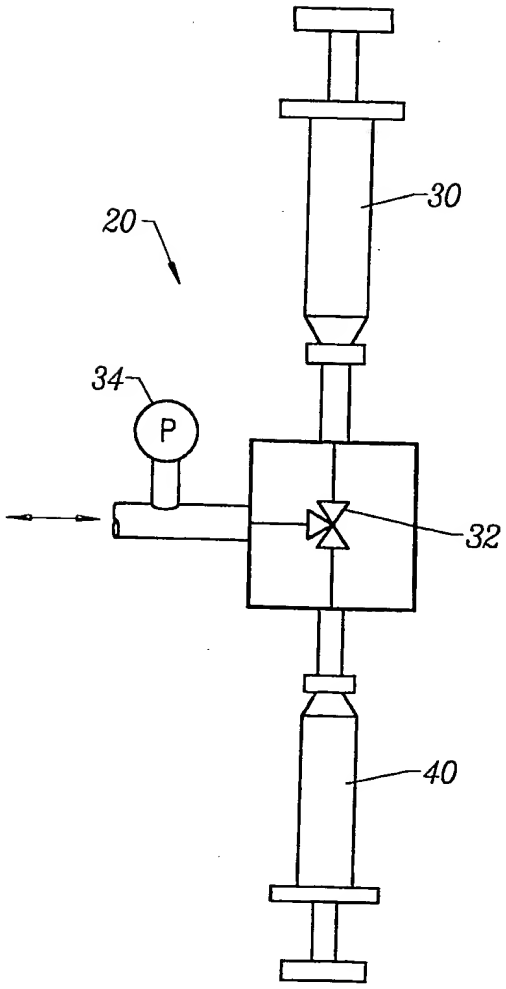


FIG. 4A

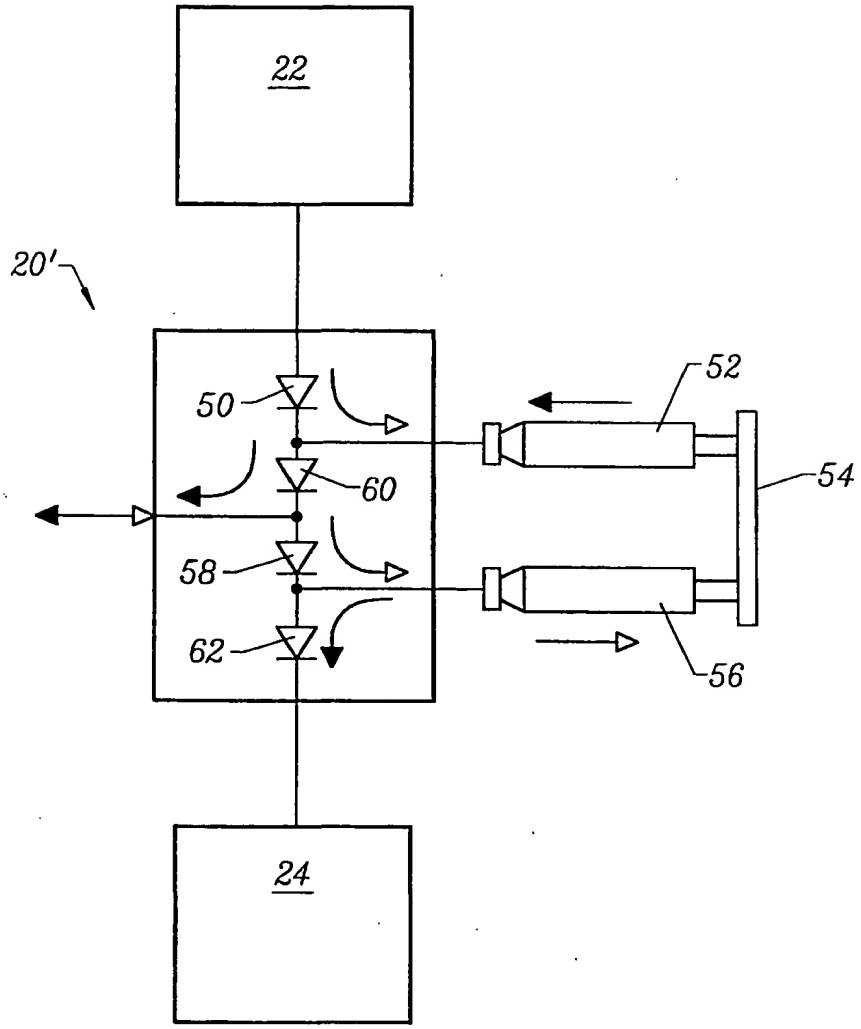


FIG. 4B

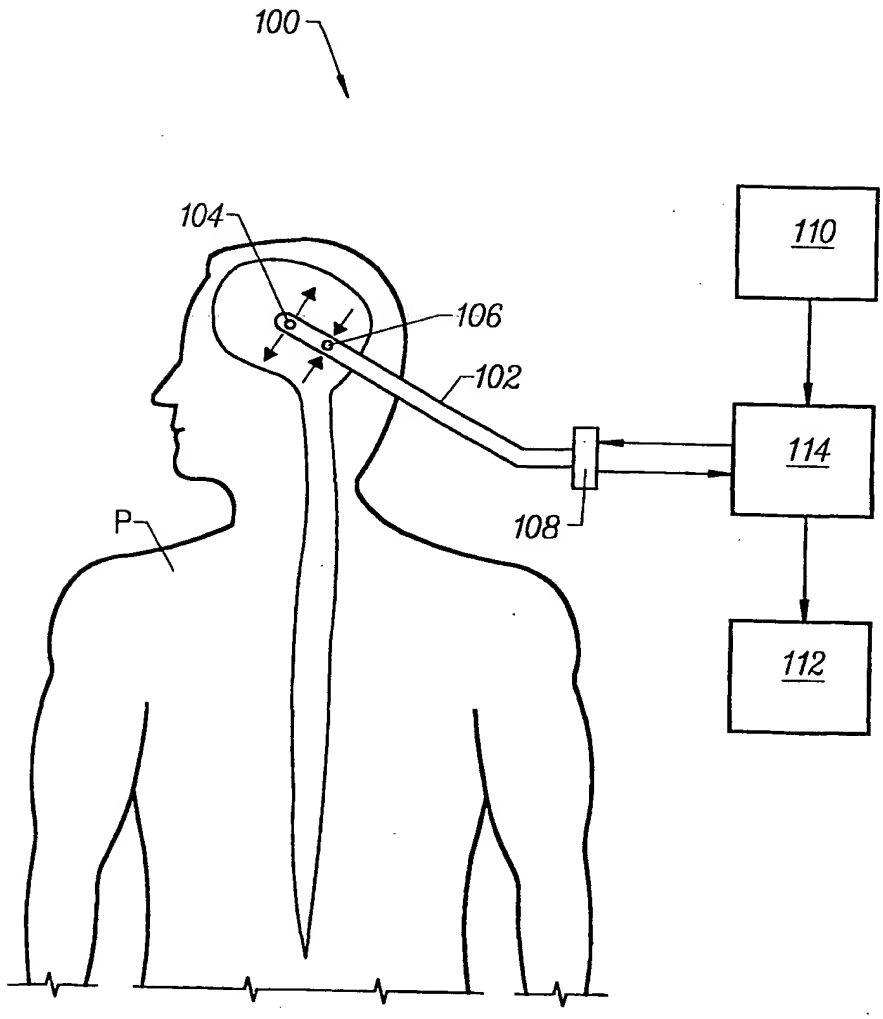


FIG. 5

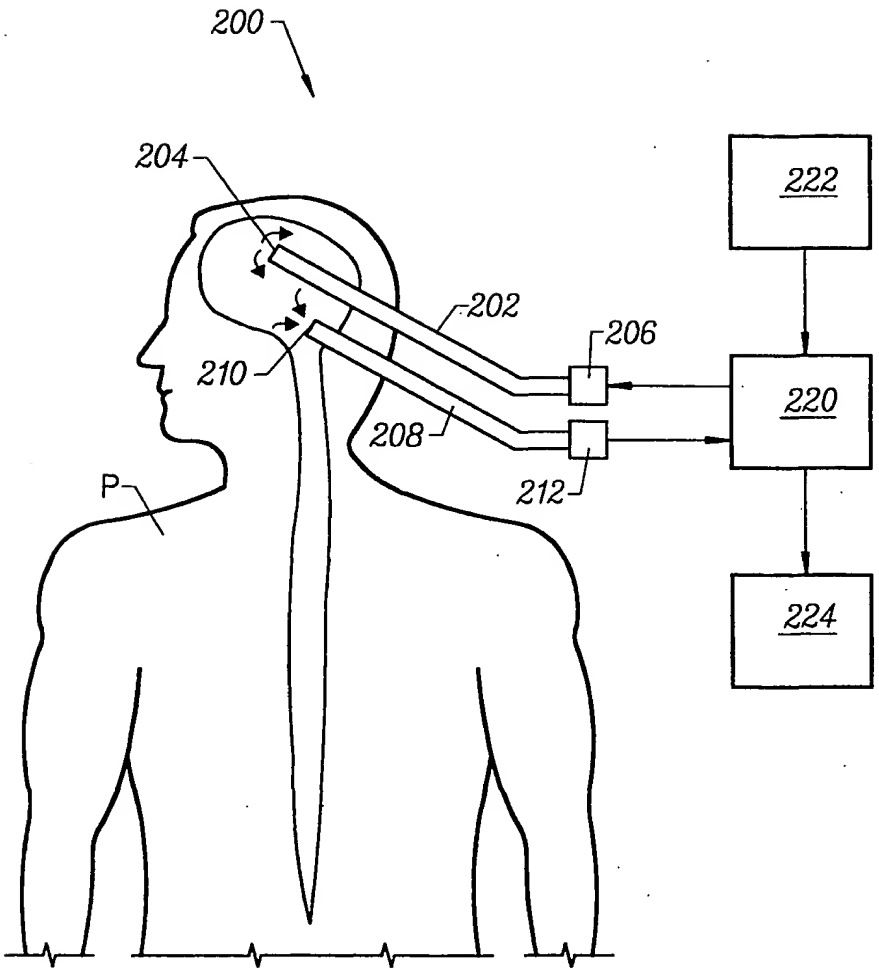


FIG. 6

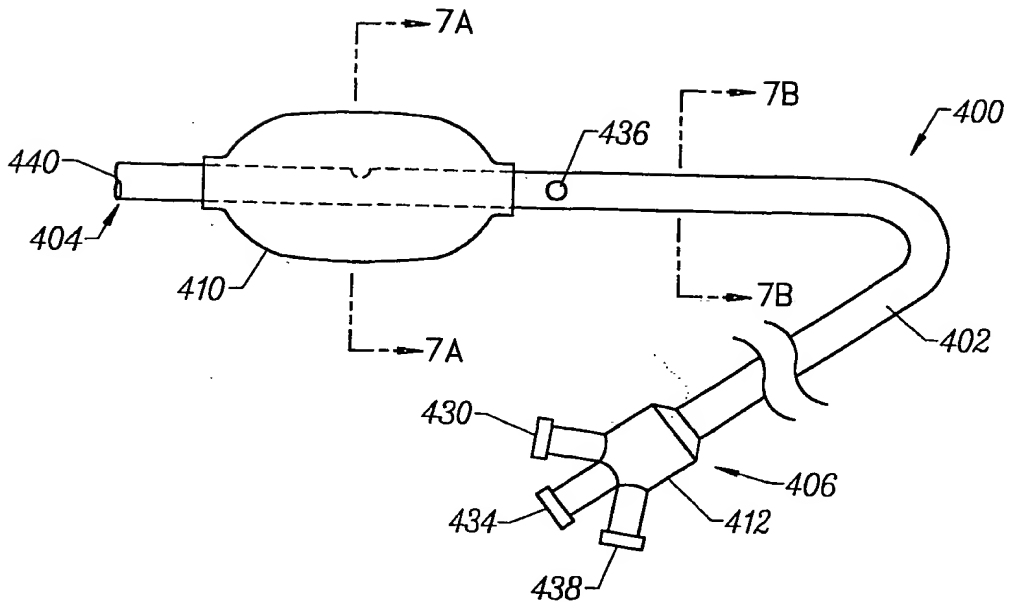


FIG. 7

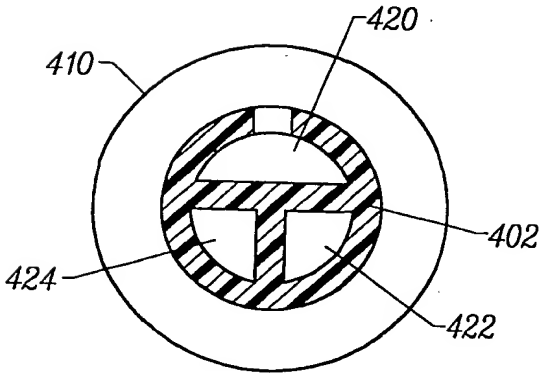


FIG. 7A

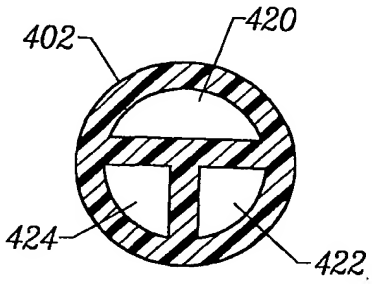


FIG. 7B

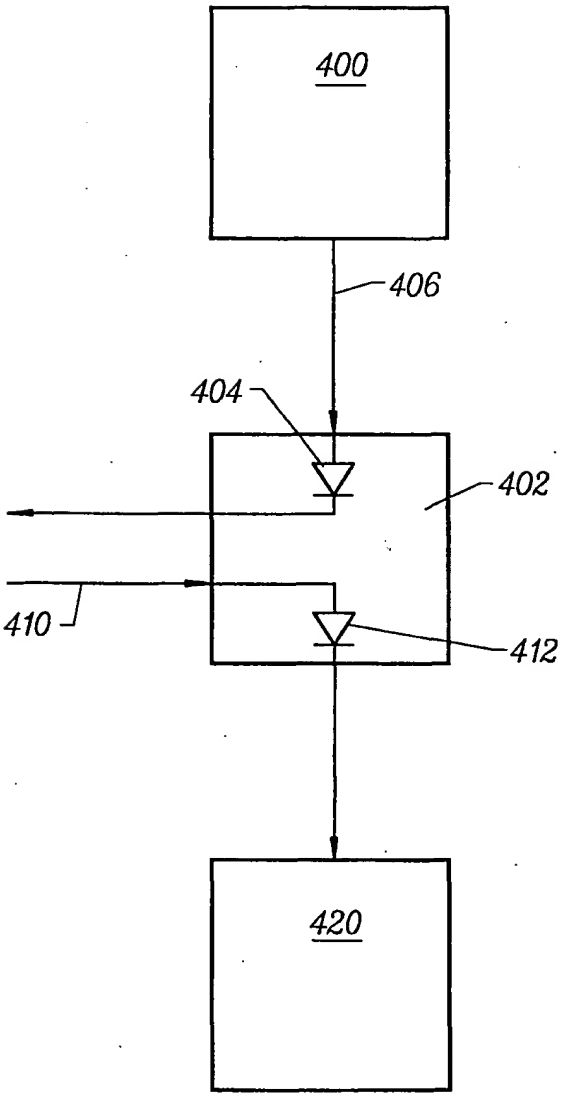


FIG. 8A

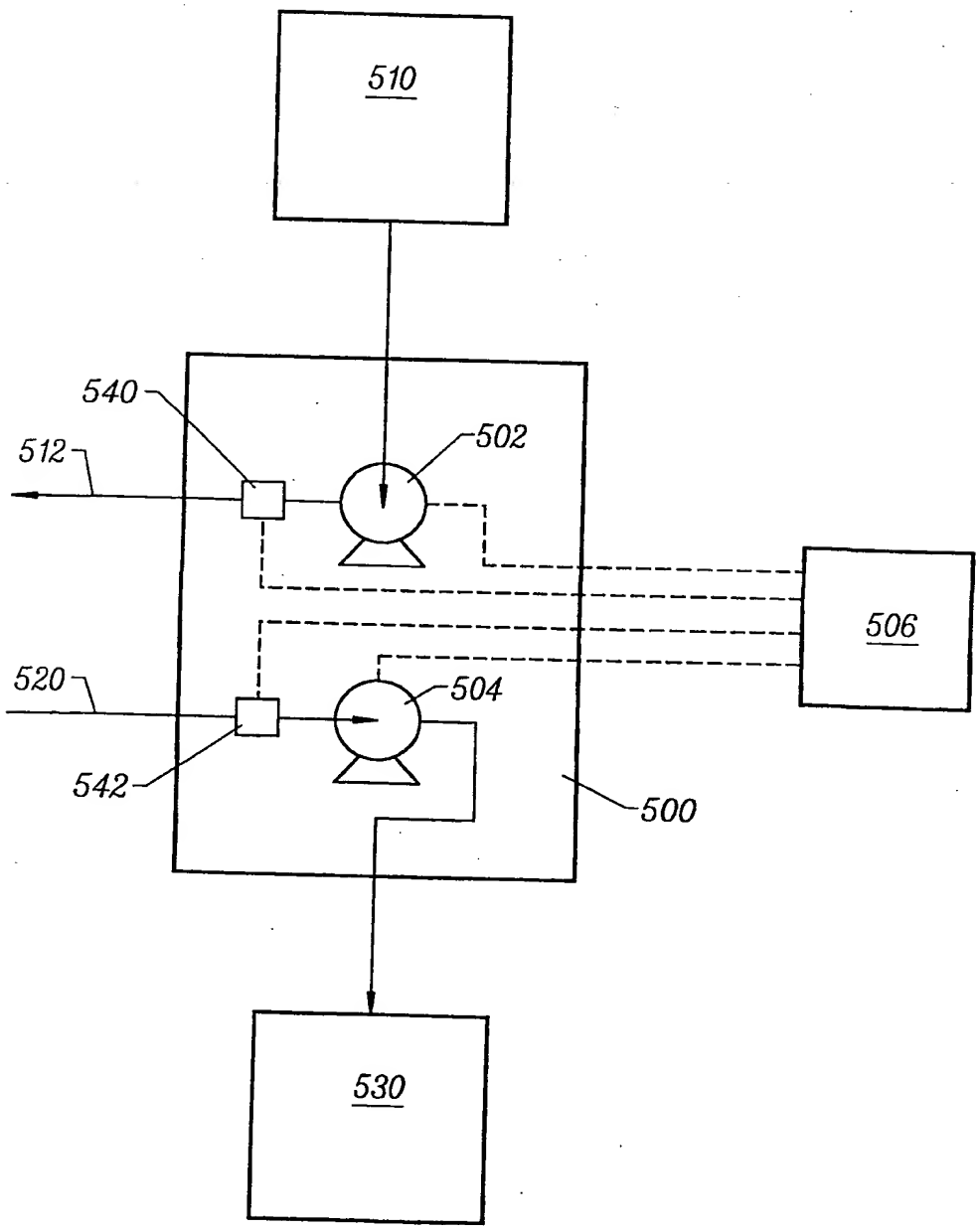


FIG. 8B

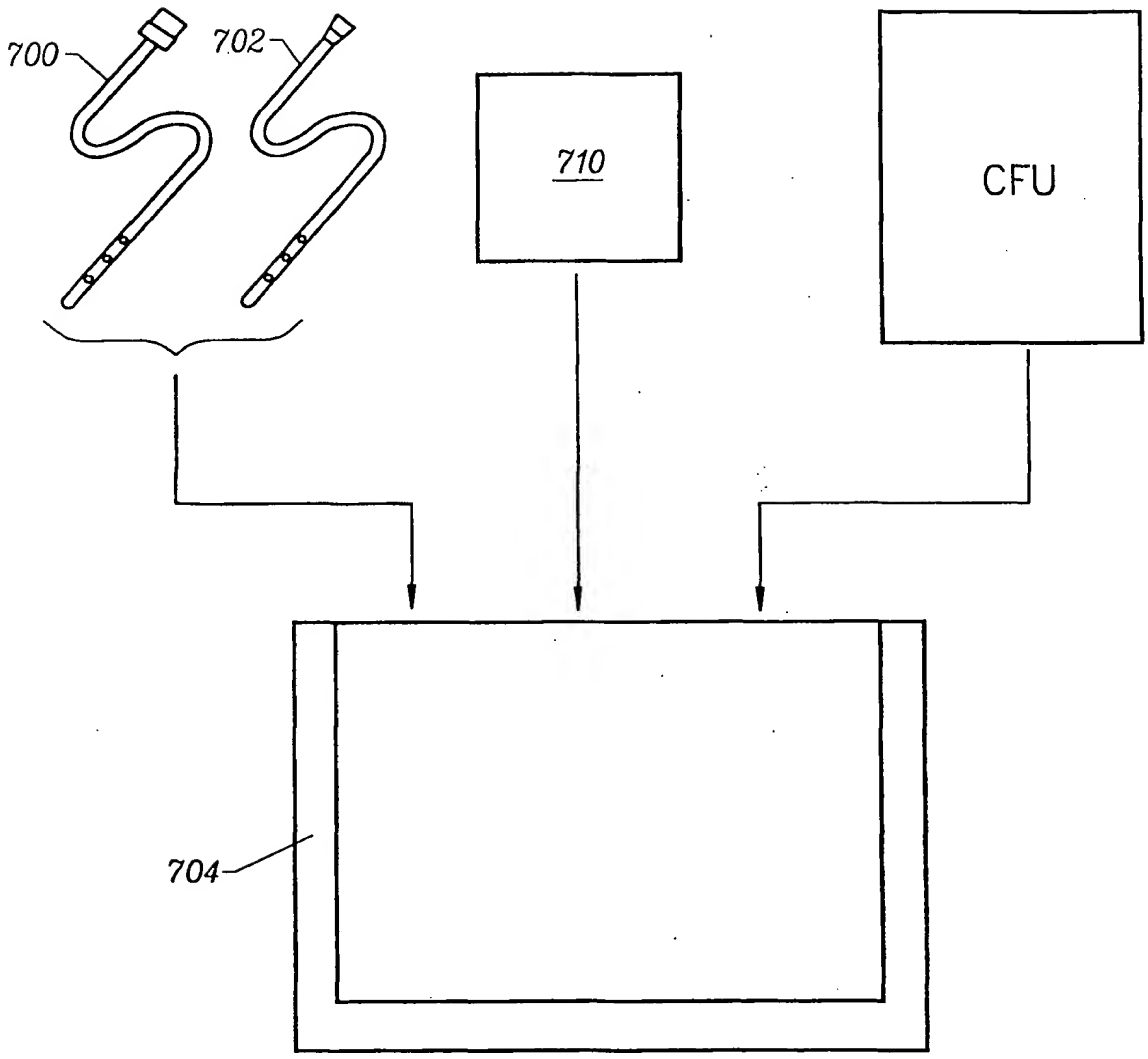


FIG. 9

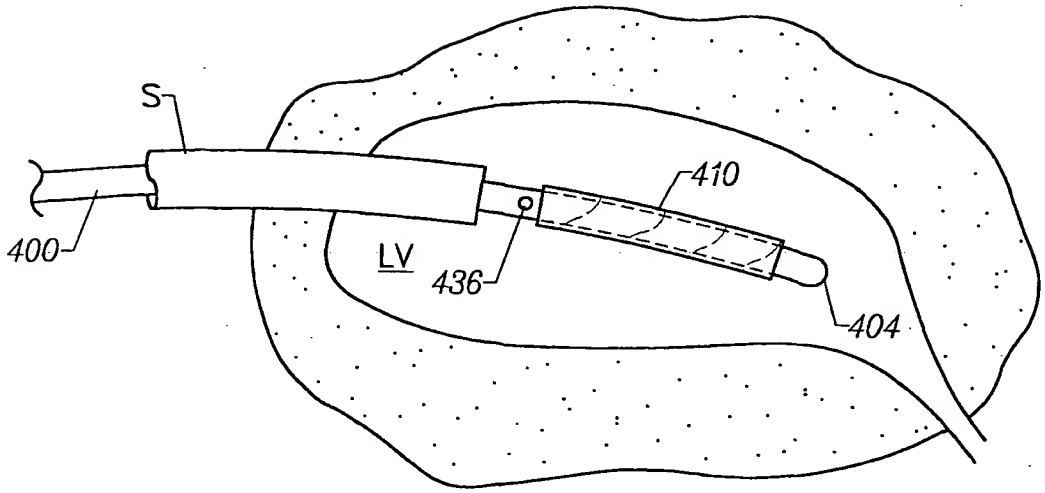


FIG. 10A

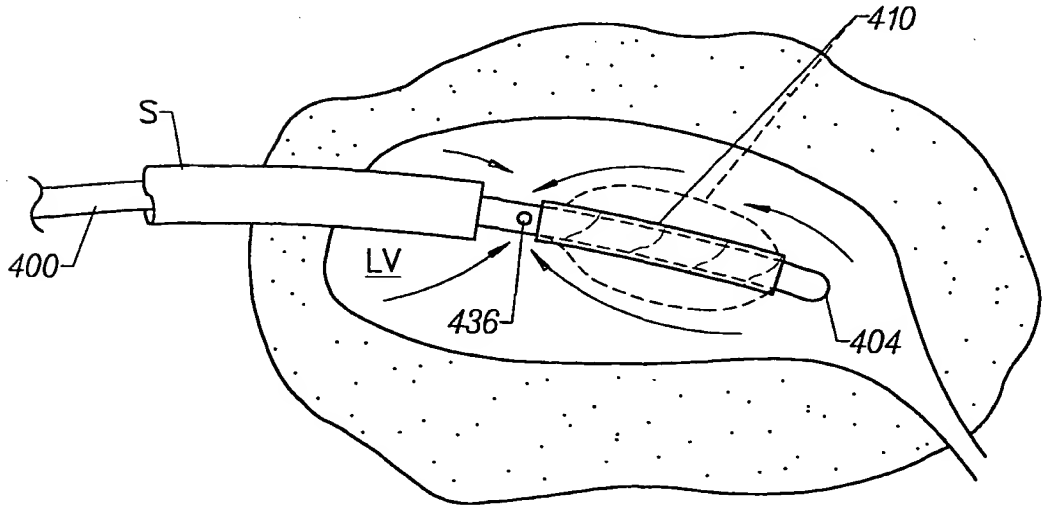


FIG. 10B

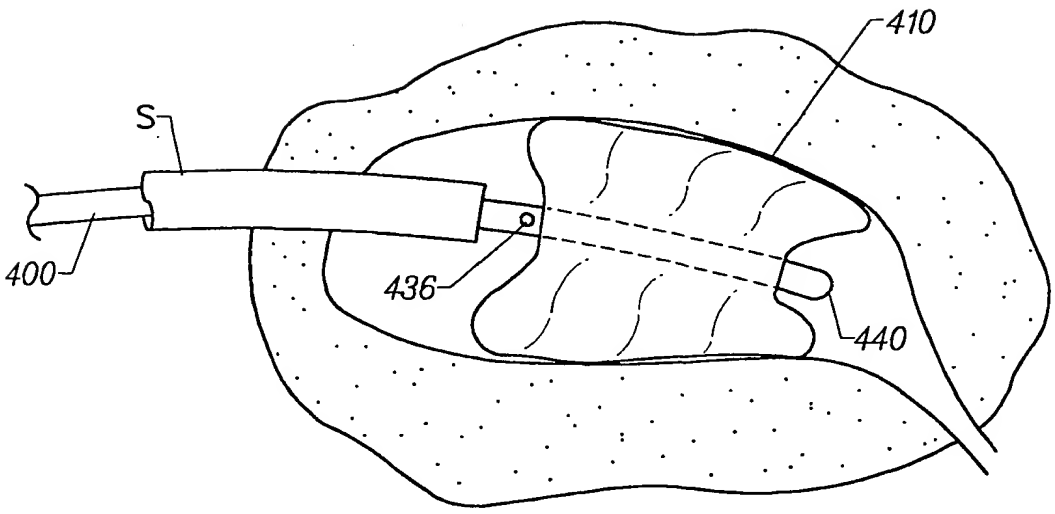


FIG. 10C

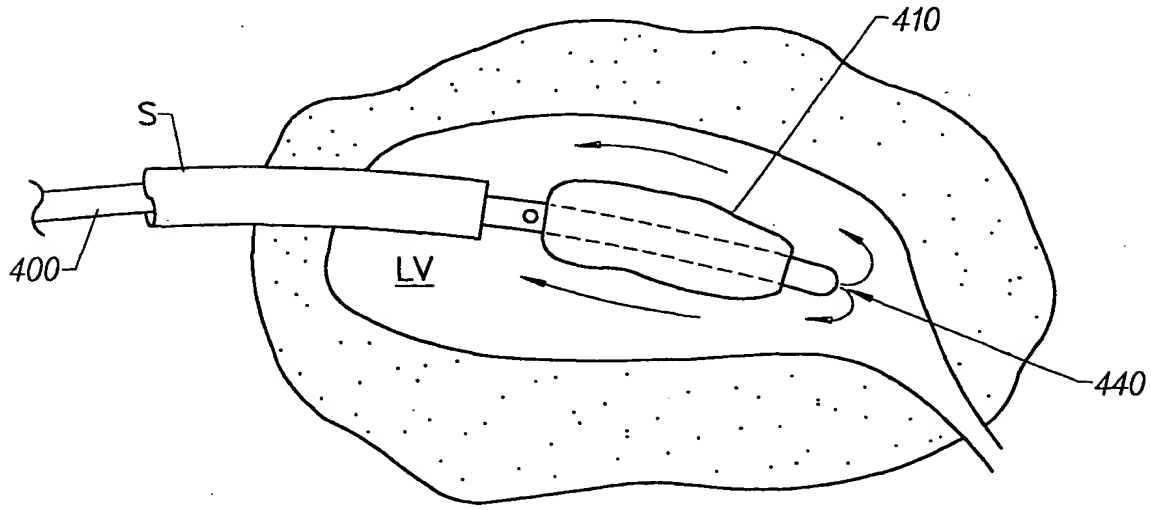


FIG. 10D

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/02275

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :A61N 1/30
US CL :604/27
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 604/8, 9, 27, 264, 500, 503, 507-509

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>---<br>Y | US 5,683,357 A (MAGRAM) 04 November 1997, col. 2 lines 32-44. | 1, 3-14<br>---<br>2, 19, 20, 22-48 |
| X<br>-----E<br>Y | US 6,042,598 A (TSUGITA et al.) 28 March 2000, Fig. 1. | 16-18<br>---<br>49-58 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

| | | | |
|---|---|---|---|
| * | Special categories of cited documents: | "T" | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| "A" | document defining the general state of the art which is not considered to be of particular relevance | "X" | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| "E" | earlier document published on or after the international filing date | "Y" | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "L" | document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "&" | document member of the same patent family |
| "O" | document referring to an oral disclosure, use, exhibition or other means | | |
| "P" | document published prior to the international filing date but later than the priority date claimed | | |

| | |
|---|---|
| Date of the actual completion of the international search<br>05 MAY 2000 | Date of mailing of the international search report<br>25 MAY 2000 |
| Name and mailing address of the ISA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. (703) 305-3230 | Authorized officer<br>KEVIN C. SIRMONS<br>Telephone No. (703) 306-5410 |

Form PCT/ISA/210 (second sheet) (July 1998)*